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Portable optical fiber probe for *in vivo* brain temperature measurements

STEFAN MUSOLINO,[1,2] ERIK P. SCHARTNER,[1,3,*] GEORGIOS TSIMINIS,[1,2] ABDALLAH SALEM,[2] TANYA M. MONRO,[1,4] AND MARK R. HUTCHINSON[1,2]

[1]*ARC Centre of Excellence for Nanoscale BioPhotonics and Institute for Photonics and Advanced Sensing, Adelaide, SA 5005, Australia*
[2]*School of Medicine, The University of Adelaide, Adelaide, SA 5005, Australia*
[3]*School of Physical Sciences, The University of Adelaide, Adelaide, SA 5005, Australia*
[4]*The University of South Australia, Adelaide, SA 5001, Australia*
[*]*erik.schartner@adelaide.edu.au*

Abstract: This work reports on the development of an optical fiber based probe for *in vivo* measurements of brain temperature. By utilizing a thin layer of rare-earth doped tellurite glass on the tip of a conventional silica optical fiber a robust probe, suitable for long-term *in vivo* measurements of temperature can be fabricated. This probe can be interrogated using a portable optical measurement setup, allowing for measurements to be performed outside of standard optical laboratories.

OCIS codes: (060.2370) Fiber optics sensors; (120.6780) Temperature; (170.6280) Spectroscopy, fluorescence and luminescence; (170.3890) Medical optics instrumentation.

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1. Introduction

The brain is the most temperature-sensitive organ in the body [1]. Brain temperature can be influenced by multiple environmental, immunological and toxicological factors, and even small deviations in brain temperature can result in profound functional behavioral impacts, regional cell toxicity within the brain or even neuronal cell death [2]. Preclinical rodent research examining acute thermal insults has relied upon the use of rectal thermometers and/or intraperitoneal telemetry sensor implants. However, when examining thermal insults such as the administration of stimulant drugs (e.g. 3,4-methylenedioxy-methamphetamine; MDMA), whose pharmacology and toxicology impact discrete brain regions deep within complex cellular structures [3], it is important to measure temperature in a localized spatial region within the brain. These requirements make the use of other available techniques impractical. As such, previous spatial resolution of brain temperature had been limited to approximately 125µm [4]. For these complex experiments there is a requirement for a minimally invasive temperature probe, which can record ± 0.1 °C changes within deep brain structures, in a live ambulatory behaving rodent, in a medical science laboratory. Optical fibers have been used as a potential solution for this, with previous work demonstrated using large diameter (0.5 mm) optical fiber probes implanted within a pig brain [5].

Optical fiber temperature sensing has traditionally relied on the interrogation of Bragg gratings inscribed on the core of the fiber to perform measurements by monitoring the shift in the wavelength of light reflected as a result of a temperature change [6]. These fiber sensors however require a significant length of fiber to obtain high efficiency [7, 8], or complex fabrication methods to obtain a sufficient reflection in a small region [9], and generally only show a coarse resolution of 1-2 °C [7, 10]. Alternative methods using resonance effects such as whispering gallery modes can also be used to measure temperature, where the resonant wavelength can be monitored and used to infer temperature [11]. These methods also require very high experimental complexity, both in the fabrication of the resonator as well as the high resolution requirements for signal analysis. In addition, these techniques are also typically cross-sensitive to local refractive index variations, which also present as a shift in the resonant wavelength.

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In recent years rare-earth thermometry has evolved as a potential solution for small-scale measurements of temperature [12, 13]. This method relies on interrogating rare-earth ions such as erbium [14], neodymium [12] or praseodymium [15] which are doped within a suitable host media. The emission spectrum from two thermally linked energy levels, appearing as two different peaks in the overall emission spectrum of the material, changes its shape as the temperature of the host medium varies [16]. This allows for the temperature to be determined by a ratiometric technique, where the intensity of emission from one band is compared to that from the second band at different temperatures. This results in a calibration of the temperature corresponding to the band ratio that is insensitive to power fluctuations [17]. Co-doping of a sensitizer such as ytterbium allows for greatly enhanced upconversion compared to a material with the same primary ion concentration [13, 18].

Typically rare-earth thermometry technique utilizes upconversion emission, where the relevant spectrum is emitted at a shorter wavelength than the excitation light [19]. This is especially important in an application involving *in vivo* measurements, as alternative optical methods which rely on excitation and collection using UV or visible light can be strongly influenced by background autofluorescence from the surrounding tissue [20]. The use of upconversion emission circumvents background signals, as the only autofluorescence generated is low-efficiency two-photon emission [21].

Our previous work on the fabrication of optical fiber probes using rare-earth doped glass for temperature sensing demonstrated a proof of concept as to the possibility of using fluorescence up conversion in biological/medical applications [22], however practical use of these sensors was limited by the use of bulk optics for coupling into the optical fiber probe, and the use of a large, benchtop spectrometer for analysis of the emitted optical signal.

In this work we build upon the technology developed in our previous paper and demonstrate a fully portable temperature measurement setup based on rare-earth doped glass optical fibers which does not require alignment of any components and can fit on a portable optical breadboard. This setup is deployed to a medical research laboratory to show preliminary results on the use of these optical fiber probes for *in vivo* preclinical measurements of brain temperature.

2. Method

2.1 Probe fabrication

The glass host material chosen was sodium zinc tellurite (ZNT) glass [23], doped with 1 mol% erbium and 9 mol% ytterbium. Co-doping with a sensitizer, in this case ytterbium, allowed for the upconversion efficiency to be significantly increased over doping solely with erbium [18, 24].

Optical fiber probes were fabricated using a previously established method [22]. One meter of polarization maintaining (PM) fiber (Nufern 980XP) was cut, and 15 mm of coating stripped from one end of the fiber. A 25 gauge needle was cut to a length of 4 mm, and any sharp edges rounded off. The fiber was then inserted into the needle, cleaved, and glued inside the needle body with approximately 2 mm of fiber protruding from the end. This fiber tip length was chosen to minimize the impact of fiber implantation on the surrounding microcirculation in tissue.

This fiber was sheathed within a standard 900 μm diameter optical fiber protective sleeve. This step was required as preliminary experiments demonstrated that an uncoated fiber was susceptible to mechanical breakage during the course of the *in vivo* measurements in live ambulatory rats. Testing demonstrated that sheathing the fiber significantly reduced the probability of fiber breakage, even during periods of high locomotion, turning and rearing activity. The sheathed fiber was then spliced using an arc splicer (Fujikura FSM-100) to a connectorized patch cable for easy integration with measurement equipment.

The coating method used to fabricate the sensing region on the fiber tips is shown in Fig. 1. Tellurite glass was used for the fabrication of the tips as the melt temperature used (820 °C) was significantly below the softening point of the silica glass fibers (≈1600 °C) so no

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deformation of the fibers is observed [22]. The fiber tip was immersed within the molten tellurite glass for a period of approximately one second, before being removed and allowed to cool in ambient atmosphere to room temperature. Probes were stored within a protective case for later use in measurements.

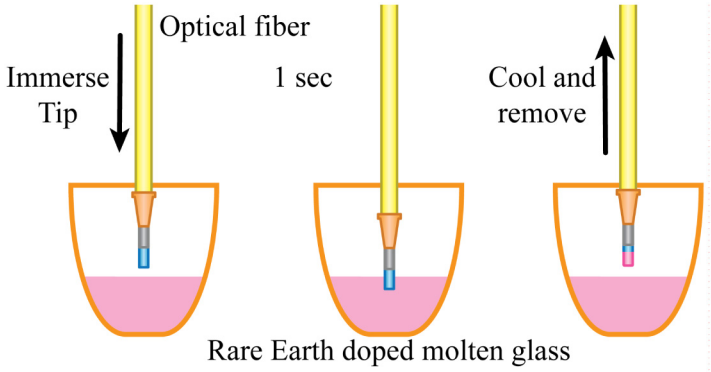

Fig. 1. Method for fabrication of temperature sensitive optical fiber tips. The fibers are cleaved and mounted within needles, and encased within a protective buffer jacket. The assembly is then dipped into erbium:ytterbium doped tellurite glass to rapidly functionalize the tip.

2.2 Optical configuration

Due to the requirement that the temperature probe be used within a medical research laboratory, without access to temperature controlled spaces or vibration-damped tables, the experimental configuration from [22] was found to be unsuitable for this application. Preliminary experiments using a portable breadboard were strongly affected by both vibrations and temperature fluctuations within the measurement space, leading to deviations between the optical probe and reference probe.

The final optical setup is shown in Fig. 2 below. The 980 nm laser source (Thorlabs BF-979-0300) was connected directly to a 99:1 PM splitter (AFW PFC-98-1), with the probe connected to the 1% output of the splitter. This configuration was chosen to minimize the potential for cell damage or local heating at the end face of the probe that could affect the validity of temperature data gathered, while maximizing the returned optical signal through the PM splitter. The output port of the splitter was passed through a short-pass filter (Semrock FF01-842) to remove the residual pump light, before being coupled into a portable spectrometer for spectral analysis (Ocean Optics QE65 Pro).

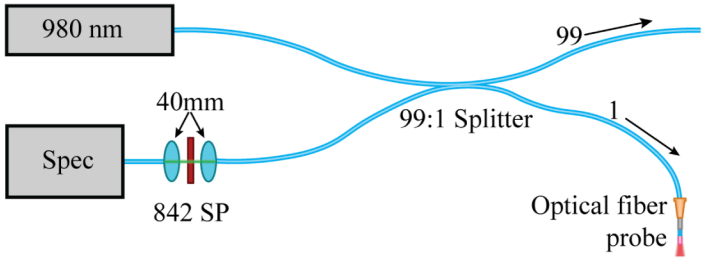

Fig. 2. Optical configuration for experimental setups to minimize the requirement for bulk optics. The short-pass filter is required to prevent backscattered pump light from saturating the detector on the spectrometer.

2.3 Probe calibration

Each probe was individually calibrated to obtain a plot of the expected fluorescence ratio versus the actual temperature. A reference resistance temperature device (RTD, Omega Class

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A 100 Ω) was utilized during measurements. The RTD was used for calibration during *in vitro* measurements, and for monitoring ambient temperatures during the *in vivo* portion of measurements. For calibration the RTD was co-located within a rats brain submerged in a water bath, with both the probe and RTD temperature cycled using an incubator. The probe was inserted into the brain tissue to better simulate the actual environment that it would experience during *in vivo* trials to ensure that the tissue in close proximity to the optical fiber tip would not influence measurements.

2.4 Animals

Four pathogen-free male Sprague-Dawley rats were used, weighing 270-300 g. All animals were supplied by the Adelaide University Laboratory Animal Services (Adelaide, South Australia). Rats were housed in temperature (18–21 °C) and light-controlled (12 h light/dark cycle; lights on at 0700 h) rooms with standard rodent food and water available *ad libitum*. Ethics approval for this study was given by the University of Adelaide Animal Ethics Committee, and all procedures were in strict accordance with the National Health and Medical Council of Australia Guidelines for the Care and Use of Laboratory Animals.

2.5 Radio telemetry implantation

Rats were anesthetized with chloral hydrate (400 mg/kg i.p.) in 0.9% saline and placed on a water-heated pad (37 °C). Once fully anesthetized, rats were surgically implanted with telemetry devices (Data Sciences International TA11CTA-F40), that measure core body temperature, activity, and ECG, as reported previously [25]. One week recovery from surgery was allowed before rats underwent optic fiber implantation and any drug treatments. A radio receiver, placed under the observation bowl, received information from the implants and transferred it to a computer that recorded the data using the Dataquest LabPro software (Data Sciences International). Radio data was recorded every 2 min over the experimental period using the experimental setup shown in Fig. 3.

2.6 Optical fiber probe implantation

Rats were anesthetized with chloral hydrate (400 mg/kg i.p.) in 0.9% saline and placed on a water-heated pad (37°C). Once fully anesthetized, the animal's head was secured in a stereotaxic frame (Kopf Instruments, Tujunga, CA, USA). After the skull was exposed, the bregma was located and the temperature probe was implanted into the right striatum (A: + 0.2 mm, L: + 3.0 mm, V: −3.5 mm from bregma). All coordinates were referenced from a rat brain atlas [26]. The temperature probe was held in place using dental cement (Vertex, Dentimex BV HJ, Zeist, Netherlands) adhered to the probe casing to form a robust attachment point to the skull. Following temperature probe implantation, rats were given 48 h to recover from surgery. A recovery period of 24 h is considered as satisfactory for microdialysis studies, as neurotransmitter levels are stabilized and interference due to surgery and anesthesia is limited [27–29]. At the end of each experiment animals were humanely killed via anesthetic overdose with chloral hydrate and brains carefully removed and stored in the freezer for future histological analysis in order to validate correct probe placement.

2.7 Drug treatments

Before the experimental day, ambulatory rats were pre-treated with 3 doses of saline (10ml/kg, i.p) over 3 days. On the experimental day, brain and body temperature recording was started at 9am (time −120), and the last saline pre-treatment injection administered at 10.30am (time −30). The temperature recordings taken between time −120 and time 0 were used to establish baseline brain and body temperature levels. At 11am (time 0), rats received the last injection of saline after which both body and brain temperature were recorded for a further 4 h until the end of the experiment. A saline drug treatment schedule was selected for experimentation to ensure low counts of animal locomotor activity (LMA) during the recording period. High LMA counts have the potential to negatively affect optical signal

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strength due to excess fiber bending and twisting during periods of increased animal movement. National Instruments LabVIEW software was used to simultaneously record both the upconversion emission from the fiber probe, as well as the ambient temperature from the RTD.

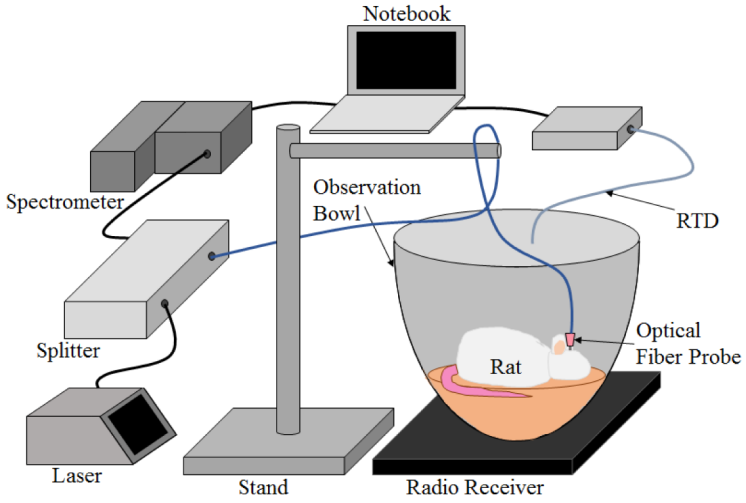

Fig. 3. Experimental set up for *in vivo* measurements to compare brain and body temperature recordings in an ambulatory animal.

3. Results

3.1 In vitro

In vitro results with the fiber probe and co-located RTD are shown in Fig. 4. These demonstrate that the measured change in fluorescence ratio over the relevant biological range can be approximated as linear with an R^2 of 0.9994 over the measured range from 22°C to 51°C, with a sensitivity of $0.00526K^{-1}$ displaying a similar response to the previously published probe that showed a precision of 0.1-0.3 °C [22]. Trials showed that minimal correlation was observed between the environmental temperature, and the temperature recorded from the optical probe even with large (>5 °C) changes in the laboratory temperature over the duration of measurements.

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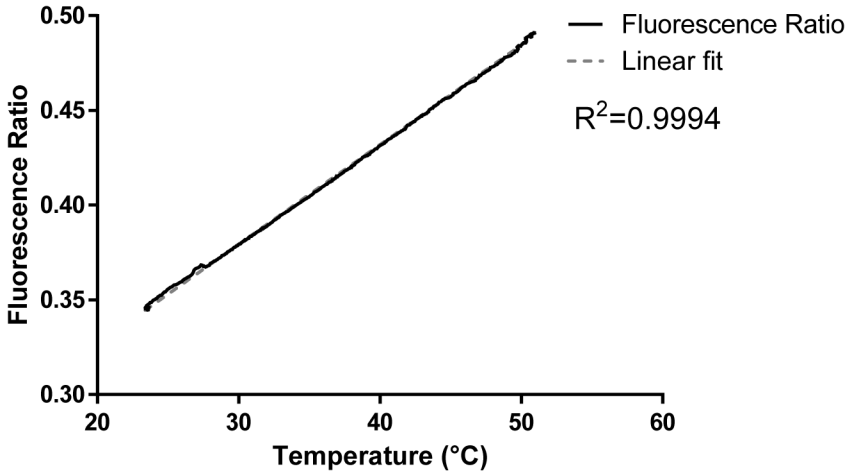

Fig. 4. *In vitro* fluorescence ratio *vs.* reference temperature for increasing temperature, R^2 = 0.9994 and a sensitivity of 0.005258K^{-1}

3.2 In vivo

Results from the implantation of a probe within an ambulatory rat brain is shown in Fig. 5(a) below. Figure 5(a) shows the brain and body temperature measurements gathered from the fiber probe and implanted telemetry device respectively in a saline treated rat, as well as laboratory ambient temperature observed from the RTD. Body, brain, and ambient temperature data are expressed as temperature change from baseline. Figure 5(b) shows the brain temperature measurements, averaged across multiple (n = 4) animals, observed with the fiber probe and body temperature measurements gathered from the implanted telemetry receiver in saline treated rats. Figure 5(b) results are shown as the mean values and standard error across all trials, at six minute intervals.

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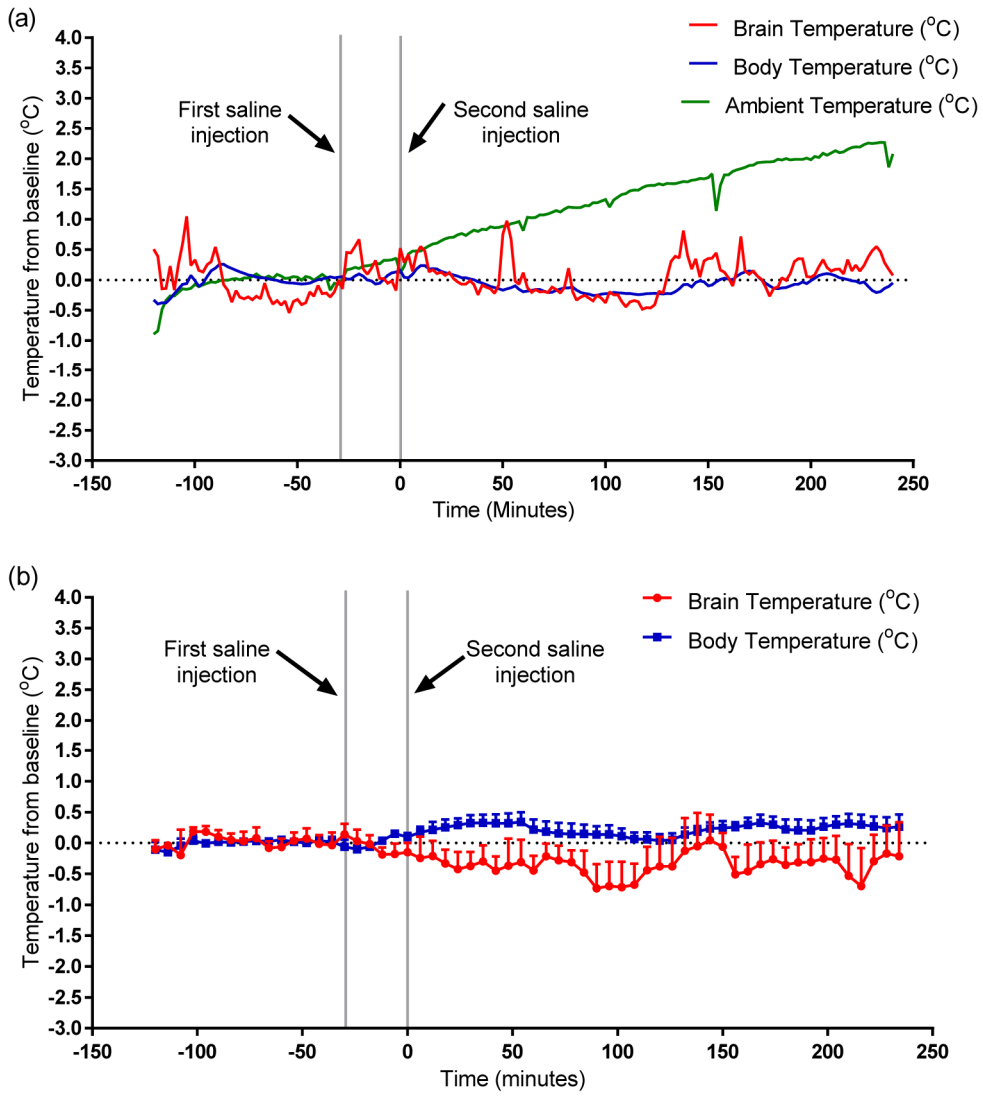

Fig. 5. (a) - *In vivo* results for fluorescence brain temperature probe, implanted body temperature monitor, and RTD ambient temperature monitor for an example saline treated rat (n = 1). Time and temperature are shown relative to the second saline injection time. The brain and ambient temperature are recorded at 10 second intervals and body temperature at 120 second intervals. (b) – *In vivo* results for fluorescence brain temperature probes, and implanted body temperature monitors (n = 4), averaged across all trials at 6 minute intervals. Error bars show the standard error in the mean.

These results demonstrate that the rare-earth doped glass optical fiber sensor is able to measure the temperature within the rat brain over an extended duration, while the rat is free to move within its enclosure. The results in Fig. 5(a) display minimal effects of ambient temperature on optic fiber probe temperature recordings as no systematic trend in the data is observed even from large changes in ambient temperature. Figure 5(b) results display a good correlation between brain and body temperature across the four trials, with both the brain and body temperatures agreeing within the error margin of the experiment.

During preliminary probe trials it was observed that some fluctuations in the overall intensity are seen as the fiber is bent too close to its critical bend radius. Due to the wavelength dependent nature of the bend loss of the fiber, these losses impact the observed

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fluorescence ratio and the corresponding observed temperature. While in preliminary trials this effect resulted in large (>1 °C) deviations from values with an un-bent fiber, the use of high durability sheathed fibers in this experiment has reduced this, allowing for stable measurements to be performed over the desired time period. Some sharp features of lower amplitude than the preliminary trials were still observed in spectral readings, which are likely due to bending of the fiber, seen as sharp spikes in the brain temperature signal in Fig. 5(a). Further improvements to the robustness of the jacketing, or the use of high numerical aperture (NA) fiber could potentially reduce this further for future trials.

4. Conclusion

We have successfully demonstrated a proof-of-principle measurements for the use of an optical fiber probe to measure temperature *in vivo* based on rare-earth thermometry. The use of the rare-earth coating on the fiber tip allows for the sensing area to be spatially localized to a thin region directly in front of the core of the fiber. Minimizing the temperature sensitive region allows for temperature to be observed at specific locations within the brain. This allows for the probe to be implanted with minimal effect on the local temperature due to the low heat conduction of the silica glass fiber compared to the metal wires within conventional thermocouples. For future measurements if improved spatial resolution is required then the fiber probe can be tapered to reduce the outer diameter, while still allowing the upconversion signal to be collected [30].

The simple fabrication method allows for rapid fabrication of the probes, with no requirement for post-processing after the tips are coated with the tellurite glass.

The use of these probes will allow for temperature to be recorded in an ambulatory animal over an extended period of time post-implantation. Preliminary results demonstrate that the probe can be monitored for a period of at least 48 h with no adverse effects, and due to the physical nature of the sensing method no photobleaching or degradation of the probe signal would be expected for long-duration recordings.

The probe could find applications to perform measurements *in situ* with other sensing elements, such as electrodes, microdialysis probes, and other neural recording equipment. Due to the small size of the fiber tip it could be affixed to an existing sensor, and implanted with an identical method to that used in existing experiments without inducing additional stress or damage. The probe is also suitable for multiplexing with other optical sensors which use visible excitation, as there should be minimal cross-talk between the sensors.

The current experimental procedure made obtaining both optical and reference brain temperature measurements *in vivo* difficult as it was not possible to co-locate the RTD reference measurement in the brain. To address this, future investigations will involve the comparison of brain temperature recorded by the optical fiber probe and a co-located brain implantable thermocouple electrode *in vivo* to more thoroughly assess the accuracy of the optical fiber probe in free-to-move animals. Continued studies will also aim to quantify the effects of fiber curvature on observed fluorescence ratio and temperature readouts of the probe in order to assess its accuracy during periods of high animal activity. Further modifications to the probe design should reduce the effects of bending and vibrations on the temperature readout, and future work will examine the use of more robust outer jacketing and high NA fibers to mitigate the variations induced from these effects.

Future investigations will use this method to assess brain and body temperatures of animals which have been administered either control injections of saline, or injections of 3,4-methylenedioxymethamphetamine (MDMA). Modifications to the experimental protocol during these investigations should allow for the implantation of multiple probes at different spatial positions within the brain. The ability to monitor temperature within different regions of the brain as well as the body should allow for an improved understanding of the hyperthermic effects of stimulant drugs, and the pathways involved in driving the drug-induced hyperthermic response. This information could aid in the development of a pharmacological intervention for acute drug toxicity for use in an emergency room setting.

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In the future, a fully developed probe could find potential application in human brain temperature monitoring after traumatic brain injury, stroke, or subarachnoid hemorrhage when the brain is extremely sensitive and vulnerable to small deviations in temperature. The probes ability to measure temperature with high temporal and spatial resolution could play a useful role in the multimodal monitoring of patients with severe head trauma in order to prevent secondary injury to the brain. It could also be utilized for tracking hypothermia in infants with neonatal encephalopathy to aid in neuroprotective therapy efforts during the first 72 hours after delivery.

The adaption of the experimental configuration to a completely portable setup with no alignment required allows for the deployment of these probes to spaces outside of conventional optics laboratories, which is an important step towards the use of these probes to examine real-world medical problems.

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